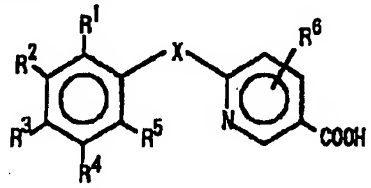
(57) (Abstract)

(Construction)

A topical agent containing a compound represented by the following formula (wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group and the like, and X denotes -NH-CO- or -CO-NH-, and R6 denotes hydrogen, 1-6C alkyl group and the like)



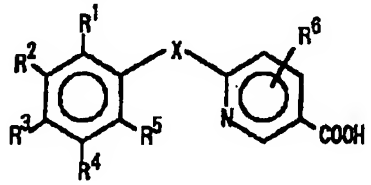
(effect)

It has excellent skin deterioration prevention action, and is stable with small percutaneous absorption, safety is high. Moreover, because it is readily metabolised, side effects due to retinoid action is small.

Patent Claims

[Claim 1]

A topical agent containing a compound represented by the following formula:



(wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group, X denotes -NH-CO- or -CO-NH-, and R6 denotes hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group).

[Claim 2]

A topical agent in accordance with Claim 1, having skin deterioration prevention action.

[Claim 3]

A topical agent in accordance with Claim 1, wherein aforesaid compound is a compound that is not substantially absorbed percutaneously.

[Claim 4]

A topical agent in accordance with the Claim 1, wherein the local and/or systemic cytotoxicity is reduced.

[Claim 5]

A skin deterioration inhibitor for topical use, containing a compound in accordance with Claim 1 as effective ingredient.

(Detailed Description of the Invention)

(0001)

(Sphere of Application in Industry)

This invention is related to a topical agent, in particular, a topical agent having skin deterioration prevention action.

(0002)

(Technology of the Prior Art)

In order to prevent skin deterioration such as wrinkling, sagging of skin and disappearance of brightness accompanying the photo-damage due to sun irradiation or aging, various topical agents have been used. In such topical agents, a component that protects the skin from the external factor such as sun, a component that acts on the skin itself and promotes activation of skin, and the like are formulated. As an effective ingredient having the latter action, Vitamin A or derivatives thereof are attracting attention.

(0003)

It is known that the retinoic acid which is an active metabolite of vitamin A (vitamin A acid) binds to a specific receptor of the target cell, and physiological effect is displayed, and the compound which binds to this receptor (retinoid receptor) and displays retinoic acid-like action is generally known generally as retinoid. Moreover, it is known that retinoid has various kinds of actions such as vision control action, growth stimulation action, reproduction action and the like, and in particular it plays an important function for the normal differentiation and maintenance of skin. In some cases, topical agent containing vitamin A and some retinoids may be topically used for the purpose of skin deterioration prevention. However, in practice, whether a rough skin, dryness, follicular hyperkeratosis and the like are inhibited by retinoid or not, or whether the effective for skin deterioration prevention or not, is not known.

(0004)

On the other hand, the retinoids sometimes used for aforesaid purpose, in general have a highly lipid soluble characteristics, and when applied as a topical agent, they are quickly absorbed to the body from the skin (percutaneous absorption), and there is a situation that systemic side effect such as hyperretinoidosis and the like are accompanied in addition to the target topical action (skin deterioration prevention action). Moreover, these retinoids were not readily decomposed locally and in vivo, and there was case that side effect due to cell injury is induced, and there are many restrictions for the application for the purpose of skin deterioration prevention.

(0005)

On the other hand, as compound having retinoid action, benzoic acid derivatives in accordance with Kokai 61-22047, Kokai 61-76440 are known. Moreover, pyridine carboxylic acid derivatives having retinoid action are disclosed in Kokai 6-263702, EP Laid-Open 617020-A1 and PCT WO93/6086. As for pyridine carboxylic acid derivatives disclosed in Kokai 6-263702 EP Laid-Open 617020-A1, usefulness as anti bone disease medicine is known as well (Kokai 7-17854), however, it has not been suggested or indicated in any of these publications that these derivatives have skin deterioration prevention action.

(0006)

As for the pyridine carboxylic acid derivatives disclosed in PCT WO93/6086, it is indicated in said publication that it is useful for therapy of dermatosis, however, there is no suggestion nor indication that these derivatives have skin deterioration prevention action. Moreover, these pyridine carboxylic acids have 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro naphthyl group or 3-adamantyl phenyl group, and has an extreme lipid soluble characteristic.

(Problems to be Overcome by this Invention)

The object of this invention is to put forward a topical agent which has excellent skin deterioration prevention action. In a further embodiment, the object of this invention is to put forward aforesaid topical agent, wherein a compound having retinoic acid action is contained as effective ingredient, and cytotoxicity is reduced. Moreover, another object of this invention is to put forward a topical agent having excellent skin deterioration prevention action which has no systemic side effect such as hyperretinoidosis.

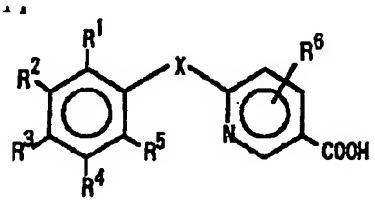
(0007)

(Means to Overcome these Problems)

These inventors carried out assiduous investigations in order to solve aforesaid problem, as a result, discovered that nicotinic acid derivatives of the following formula having activity of retinoic acid had extremely excellent skin deterioration prevention action. Moreover, these inventors also discovered that these compounds were comparatively hydrophilic, had little percutaneous absorption properties, and also were readily decomposed on skin and in vivo, therefore systemic cytotoxicity was remarkably reduced. This invention was completed on the basis of aforesaid findings.

(0008)

In other words, this invention puts forward a topical agent containing a compound represented by the following formula:



(wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group, X denotes -NH-CO- or -CO-NH-, and R6 denotes hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group).

(0009)

In accordance with the preferred form of aforesaid invention, aforesaid topical agent having skin deterioration prevention action, aforesaid topical agent wherein, aforesaid compound is a compound which is not substantially absorbed percutaneously, and aforesaid topical agent wherein topical and/or systemic cytotoxicity is reduced, are put forward. Moreover, in accordance with another form of this invention, a skin deterioration inhibitor for topical use containing aforesaid compound as effective ingredient is put forward.

(0010)

In aforesaid compound contained in topical agent of this invention, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group. As C1-6 alkyl group, either of straight chain or branched alkyl group may be used, and as further example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, tert butyl group, n-pentyl group, iso pentyl group, neopentyl group, n-hexyl group and the like can be used. Among these, ethyl group, isopropyl group or tert butyl group is preferably used. As C1-6 alkoxy group, either of straight or branched chain alkoxy group may be used, and as a

further example, methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, sec-butoxy group, tert butoxy group and the like can be used. As halogen atom, any of fluorine atom, chlorine atom, bromine atom or iodine atom may be used.

(0011)
For example, among such compounds, a compound in which two adjacent or non-adjacent substituents selected from the aforesaid R1, R2, R3, R4 and R5 are same or different alkyl groups is a preferred compound as the component of topical agent of this invention. For example, a compound in which R2 and R3, or R2 and R4 are both alkyl groups is preferred. Among such compounds, the compound wherein the alkyl group is ethyl group, isopropyl group or tert butyl group is more preferred, and methylene group is particularly preferred.

(0012)
R6 denotes hydrogen atom, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group. As C1-6 alkyl group, halogen atom or C1-6 alkoxy group, aforesaid species can be used. R6 can be substituted at arbitrary position of 2-position, 5-position or 6-position of pyridine ring. Among these the compound in which R6 is hydrogen atom is preferred.

(0013)
In more concrete terms, as component of topical agent of this invention, compounds such as 6-(3,4-diethylphenyl carbamoyl) nicotinic acid, 6-(3,4-diethylphenyl carboxamide) nicotinic acid, 6-(3,5-di-t-butylphenyl carbamoyl) nicotinic acid or 6-(3,5-di-t-butylphenyl carboxamide) nicotinic acid and the like are preferred, but the component of topical agent of this invention is not restricted to these preferred compounds. Moreover, in topical agent of this invention, one or more of aforesaid compounds can be used in a combination thereof. Moreover, arbitrary base addition salt and arbitrary hydrate of aforesaid compound may be used. For example, as base addition salt, sodium salt, metal salt such as potassium salt, calcium salt, magnesium salt and ammonium salt, organic amine salt and the like can be used.

(0014)
The quantity formulated of the aforesaid compound is not restricted in particular in topical agent of this invention, and it can be suitably varied depending on the type of the compound, application purpose and the state of skin, but in general it is 0.005-5.0 wt.% in total quantity of topical agent, preferably 0.05-1.0 wt.%. Moreover, in general, if the quantity formulated of aforesaid compound is less than 0.005 wt.%, there is a situation that the effect is not sufficient, and moreover even when the

quantity formulated exceeds 5.0 wt.%, the enhancement of the potentiation of skin deterioration prevention effect is not observed in some cases, therefore, it is not preferred to be greatly deviated from aforesaid range.

(0015)
A part of the aforesaid compound is well known compound, and for example, it can be readily produced by the method described in Kokai 6-263702 and EP Laid-Open 617020-A1. Moreover, the novel compounds can be readily produced by a person skilled in the art in accordance with processes in Examples of this specification or in aforesaid publication, furthermore by referring to process in accordance with publications such as Kokai 7-17854 and PCT WO 93/6086 in addition to these.

(0016)
In addition to aforesaid to topical agent of this invention, other components used for topical agent such as usual cosmetics, pharmaceutical agent, over the counter drug and the like, can be used. For example, vitamin B2 species such as riboflavin, riboflavin butyrate, flavin adenine dinucleitide and the like, vitamin B6 species such as pyridoxine hydrochloride, pyridoxine dioctanoate and the like, vitamin C species such as L-ascorbic acid, L-ascorbic acid dipalmitate, L-ascorbic acid-2-sodium sulphate and the like, pantothenic acid species such as calcium pantothenate, D-pantotenyl alcohol, pantotenyl ethyl ether, acetyl pantotenyl ethyl ether and the like, vitamin D species such as ergocalciferol, cholecalciferol and the like, nicotinic acid species such as nicotinic acid, nicotinamide, benzyl nicotinate and the like.

(0017)
vitamin E species such as alpha-tocopherol, tocopherol acetate, DL-alpha-tocopherol nicotinate, DL-alpha-tocopherol succinate and the like, vitamin species such as vitamin P, biotin and the like, amino acids and amino acid derivatives such as glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid and salts thereof, glutamic acid and salts thereof, lysine, arginine, cysteine, cystine, methionine, phenylalanine, tyrosine, histidine, tryptophan, proline, N-acyl acidic amino acid salt such as N-palmitoyl L-aspartic acid diethyl, N-coconut oil fatty acid-L-sodium glutamate and the like, acyl neutral amino acid salt such as coconut oil fatty acid sarcosine triethanolamine, lauroyl methyl-beta-alanine sodium and the like, pyrrolidone carboxylic acid and salts thereof, POE(40) hardened castor oil mono pyroglutamate mono iso stearic acid diester, N-coconut oil fatty acid -L-arginine ethylester -DL-pyrrolidone carboxylic acid salt and the like.

(0018)

Oil such as avocado oil, palm oil, peanut oil, beef tallow, rice bran oil, jojoba oil, evening primrose oil, carnauba low, lanolin, liquid paraffin, squalane, palmitic acid iso stearyl, iso stearyl alcohol, tri-2-ethyl hexanoic acid glycerol and the like, moisturizing agent such as glycerine, sorbitol, polyethyleneglycol, 1,3-butylene glycol, collagen, hyaluronic acid, chondroitin sulfate, dextran sulfate sodium and the like, antioxidant such as sodium erythorbate, para hydroxyanisole and the like, detergent such as stearyl sodium sulfate, cetyl sulfuric acid diethanolamine, cetyltrimethylammonium saccharin, iso stearic acid polyethyleneglycol, arachic acid glyceryl, diglycerol di iso stearate, phospholipid and the like, preservatives such as ethylparaben, butyl para pen and the like.

(0019)

Antiphlogistic such as glycyrrhizin acid derivative, glycyrrhetinic acid derivative, salicylic acid derivative, hinokitiol, zinc oxide, allantoin and the like, beautfiying and whitening agent such as placenta extract, glutathione, Saxifraga extract and the like, extract such as Phellodendron, Coptis, Shikon, peony, sialid, birch, sage, loquat, carrot, aloe, Malva sylvestris, iris, grape, coix, sponge gourd, lily, saffron, Cnidium officinale, ginger, Hypericum erectum, Ononis, rosemary, garlic and the like, activator such as a royal jelly, photo sensitive element, cholesterol derivatives, calf blood extract and the like, blood circulation accelerating agent such as gamma-oryzanol and the like, anti-seborrhoica agent such as sulphur, thianthol and the like, thickener such as carboxy vinyl polymer, carboxymethylcellulose, carboxy hydroxypropylcellulose and the like, flavour, water, alcohol, colour agent such as titanium yellow, casamine, safflower red and the like, or resin powder such as polyethylene, nylon and the like. These can be suitably formulated in accordance with requirements.

(0020)

An effective ingredient of drug useful for prevention and treatment of dermatosis and/or UV absorbent useful for prevention of photo damage and the like may be formulated to the topical agent of this invention. As effective ingredient of such drug, for example, steroidal compound and antibiotics and the like are nominated. As UV absorbent, cinnamic acid series UV absorbent such as para methoxy cinnamic acid-2-ethoxyethyl, para methoxy cinnamic acid isopropyl ester, diisopropyl cinnamate, para methoxy cinnamic acid ethylhexyl, dipara methoxy cinnamic acid mono -2-ethyl hexanoic acid glyceryl, methoxy cinnamic acid octyl and the like, benzoyl methane series UV absorbent such as butyl methoxybenzoyl methane, 4-tert butyl-4'-methoxy-dibenzoyl-methane and the like, benzophenone series UV absorbent such as glyceryl-mono-2-ethyl hexanoyl-di-para methoxybenzophenone, 2,2'-dihydroxy-4-methoxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxy

benzophenone, 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxybenzophenone-5-sodium sulphonate and the like can be used.

(0021)

Benzoate system UV absorbent such as ortho aminobenzoic acid methyl ester, para dimethylaminobenzoic acid -2-ethylhexyl ester, para dimethylaminobenzoic acid octyl ester and the like, benzoate system UV absorbent such as glyceryl p-amino benzoate, amyl-para-dimethylamino benzoate, ethyl-4-bis hydroxypropyl amino benzoate and the like, other UV absorbent such as 2-ethylhexyl -2-cyano-3,3'-diphenyl acrylate, digalloyl trioleate, salicylic acid-2-ethylhexyl, salicylic acid homo methyl, guaiazulene, urocanic acid and the like can be sued.

(0022)

Topical agent of this invention has an action of preventing the skin deterioration such as wrinkling, sagging of skin and disappearance of brightness accompanying the photo-damage due to sun irradiation or aging. Accordingly, by applying topical agent of this invention to the daily repair of skin and after sunbathing, deterioration of skin can be prevented, and youthful and healthy state of skin can be maintained. Moreover, agent form of topical agent of this invention is not restricted in particular, and for example agent forms such as solubilisation system such as toner and the like, emulsification system such as milky lotion, cream and the like, or ointment, dispersant, aerosol can be formed. Method of use is not restricted in particular, however, in the case of formulation such as cream agent, a suitable quantity is taken with a finger, and it is applied thinly and thoroughly to face and hand and preferably if it is rubbed into skin by massaging. Below, this invention is further described in concrete terms by Example, however, this invention is not restricted to these Examples.

(0023)

(Examples)

(1) Production of compound.

Example 1: 6-(3,4-diethylphenyl carbamoyl) nicotinic acid.

A liquid mixture of concentrated sulfuric acid 8.1 ml and nitric acid (d = 1.42) 5.16 ml was dropwise-added at 0 degrees to 1,2-diethylbenzene 9.96 g (74.3 mmol) and it was reacted at the same temperature for two hours. The reaction liquor was discharged into ice, and extraction was carried out with ether. The organic layer was washed with water 3 times, with saturated aqueous sodium bicarbonate and with saturated aqueous sodium chloride solution in this order, and the solvent was

eliminated by distillation after dehydration. The residue was purified by silica gel column chromatography (Fuji silica, BW-820MH, 500 g, eluent n-hexane / methylene chloride = 19/1), and 3,4-diethyl nitrobenzene 7.8 g was obtained (yield = 58.6 %). Aforesaid 3,4-diethyl nitrobenzene 6 g (36 mmol) and 5 % Pd/c 0.6 g were added to ethanol 100 ml, and catalytic reduction was carried out at normal temperature and normal pressure. The catalyst was eliminated by filtration, thereafter the solvent was eliminated by distillation, and 3,4-diethylamino benzene 4.89 g was obtained (yield: 91.2 %).

(0024)

3-methoxycarbonyl pyridine-2-carboxylic acid 4.62 g (25 mmol) was added to anhydrous benzene 500 ml and thionyl chloride 77 ml and it was reacted for six hours under reflux. The solvent was eliminated by distillation, anhydrous benzene 100 ml was added to the residue, and thionyl chloride was azeotropically-concentrated (three times). Anhydrous benzene 385 ml was added to the residue and dissolution caused, and 3,4-diethylamino benzene 4.5 g (25 mmol) dissolved in dried pyridine 19.2 ml and anhydrous benzene 385 ml was dropwise added to this solution and mixed at room temperature, and it was reacted for three hours under a stream of argon. The reaction liquor was added to iced water 1925 ml, 2 N HCl 77 ml was added and stirred well, and it was extracted three times with ethyl acetate 1.2 l. The organic layer was washed with saturated aqueous sodium chloride solution 1.2 l, thereafter it was dried with magnesium sulfate, and it was concentrated and dried to a solid. The residue was purified by silica gel column chromatography (Fuji silica, BW-820MH, 500 g, eluent ethyl acetate / n-hexane = 1/3), and crude product 7.57 g was obtained. The obtained product was recrystallised from n-hexane / ethyl acetate, and 6-(3,4-diethylphenyl carbamoyl) nicotinic acid methyl ester 6.35 g was obtained (yield: 81.4 %).

(0025)

6-(3,4-diethylphenyl carbamoyl) nicotinic acid methyl ester 6 g (19.2 mmol) was dissolved in methanol 1 l, and 2 N NaOH 200 ml was added and reacted at room temperature for 12 hours. The reaction liquor was added to 0.5 N HCl 1.2 litre and extracted three times with ethyl acetate 1.2 l. The organic layer was washed with saturated aqueous sodium chloride solution 1.2 l, thereafter dried with magnesium sulfate, and solvent was eliminated by distillation. The residue was recrystallised from ethyl acetate / ethanol, and 6-(3,4-diethylphenyl carbamoyl) nicotinic acid 2.9 g was obtained (yield: 50.7 %).

Straw-coloured needle-like crystal, mp 174-176 degrees.

1H NMR (400 MHz, DMSO-d6, 30 degrees) delta: 10.57 (s, 1H), 9.16 (d, 1H, J = 2 Hz), 8.50 (dd, 1H, J = 2 Hz, 8 Hz), 8.25 (d, J = 8 Hz), 7.71 (d, 1H, J = 2 Hz), 7.67 (dd, 1H, J = 2 Hz, 8 Hz), 7.14 (d, J = 8 Hz), 2.61 (m, 4H), 1.19 (t, 3H, J = 7.5 Hz), 1.16 (t, 3H, J = 7.5 Hz)
Elemental analysis (C17H18N2O3): theoretical value C 68.44; H 6.08; N 9.39, experimental value C 68.70; H 6.11; N 9.41.

(0026)
Example 2:. 6-(3,4-diethylphenyl carboxamide) nicotinic acid.
nitromethane solution (60 ml) of acetyl chloride 6.44 g (82.0 mmol) and 1,2-diethylbenzene 9.50 g (70.8 mmol) was added dropwise into nitromethane solution (60 ml) of aluminium chloride (AlCl3) 11.4 g (62.2 mmol) and mixed at 0 degrees over a period of one hour. The reaction liquor was stirred at room temperature for two hours, and it was discharged into iced water 150 ml. Ethyl acetate 150 ml was added to this mixture, it was filtered with celite, and the aqueous layer was extracted with ethyl acetate (100 ml). The ethyl acetate layer was recovered, washed successively with water, saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride solution (for each 100 ml), thereafter it was dried with sodium sulfate and the solvent was eliminated by distillation. Vacuum distillation (bp 95 degrees /1.2 mm Hg) was carried out of the residue, and 3,4-diethyl acetophenone 12.0 g was obtained (yield: 96 %).

(0027)
Mixed liquor of 5% NaOCl solution (275 ml) and 25% NaOH solution (33 ml) was added dropwise and mixed to dioxane (160 ml) solution of 3,4-diethyl acetophenone 11.0 g (62 mmol) and it was reacted at 50-60 degrees for two hours. The reaction liquor was cooled and discharged into iced water 1 l, and NaHSO3 was added and thereafter it was adjusted to pH 3 with concentrated hydrochloric acid. This mixture was extracted with ethyl acetate (750 ml, 500 ml). The ethyl acetate layer was washed with water and saturated aqueous sodium chloride solution (for each 500 ml), dried with sodium sulfate, and the solvent was eliminated by distillation. Obtained crude product 11.0 g was recrystallised from n-hexane 120 ml, and 3,4-diethyl benzoic acid 10.2 g was obtained (yield: 92 %).

(0028)
Thionyl chloride 28 ml was added to anhydrous benzene (200 ml) solution of 3,4-diethyl benzoic acid 6.5 g (36.5 ml) and it was reacted under reflux for five hours. The reaction liquor was concentrated, thereafter it was substituted twice with anhydrous benzene 50 ml and it was concentrated. Dried THF 25 ml was added to the residue and dissolved, and this solution was added

dropwise and mixed at room temperature to dried THF solution (300 ml) of 6-amino nicotinic acid methyl ester 5.55 g (36.5 ml) and triethylamine 4.61 g (4.56 mmol). The reaction liquor was stirred at room temperature for three hours. The reaction liquor was concentrated, and ethyl acetate (150 ml) and water (100 ml) were added. The aqueous layer was extracted with ethyl acetate (50 ml x 2), ethyl acetate layer was washed with water and saturated aqueous sodium chloride solution (100 ml each), it was dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography (BW-820MH, 300 g, eluent methylene chloride / ethyl acetate = 15/1), and 9.0 g mixture of 6-(3,4-diethylphenyl carboxamide) nicotinic acid methyl ester and diamide body was obtained.

(0029)

This mixture was dissolved in methanol (650 ml), concentrated hydrochloric acid (20 ml) was added and it was reacted at 55 degrees for two hours 30 minutes. The reaction liquor was concentrated, saturated aqueous sodium bicarbonate (400 ml) and methylene chloride (200 ml) were added, and the aqueous layer was extracted with methylene chloride (150 ml, 100 ml). The methylene chloride layer was washed with water, dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography (BW-820MH, 250 g, eluent benzene / acetone = 30/1), and crude product 5.5 g was obtained. This product was recrystallised from n-hexane (100 ml), and 6-(3,4-diethylphenyl carboxamide) nicotinic acid methyl ester 4.7 g was obtained (yield: 41 %).

(0030)

6-(3,4-diethylphenyl carboxamide) nicotinic acid methyl ester 4.7 g (15 mmol) was dissolved in methanol (900 ml) and 2 N NaOH 170 ml was added and reacted at room temperature for 12 hours. The reaction liquor was added to 0.5 N HCl (1270 ml) and extracted with ethyl acetate (6 l, 2 l) The organic layer was washed with saturated aqueous sodium chloride solution (2 l), thereafter it was dried with sodium sulfate, and solvent was eliminated by distillation. The residue was recrystallised from chloroform / ethanol = 1/1 (720 ml), and 6-(3,4-diethylphenyl carboxamide) nicotinic acid 2.4 g was obtained (yield: 54 %).

Colourless needle-like crystal, mp 294-295 degrees.

1H NMR (400 MHz, DMSO-d6, 30 degrees) delta: 11.02 (s, 1H), 8.88 (m, 1H), 8.32 (br d, 1H, J = 8 Hz), 8.30 (dd, 1H, J = 2 Hz, 8.8 Hz), 7.88 (d, 1H, J = 2 Hz), 7.82 (dd, 1H, J = 2 Hz, 8 Hz), 7.30 (d, 1H, J = 8 Hz), 2.69 (q, 4H, J = 7.5 Hz), 1.23 (t, 3H, J = 7.5 Hz), 1.19 (t, 3H, J = 7.5 Hz), 1.23 (t, 3H, J = 7.5 Hz), 1.19 (t, 3H, J = 7.5 Hz) z

Elemental analysis (C17H18N2O3): theoretical value C 68.44; H 6.08; N 9.39, experimental value C 68.25; H 6.08; N 9.10.

(0031)

Example 3: 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid.

A mixture of 3,5-di-tert-butyl benzoic acid (1,800 mg), thionyl chloride (3 ml) and anhydrous benzene (20 ml) was refluxed for six hours. Solvent and excess thionyl chloride were distilled under reduced pressure. The residue was dissolved in anhydrous benzene (15 ml) and a mixture of 6-amino nicotinic acid methyl (500 mg), triethylamine (3 ml), anhydrous benzene (10 ml) was added and it was reacted at room temperature overnight. The reaction liquor was introduced into water, and extraction was carried out with ethyl acetate. The organic layer was washed with water and dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography, and a mixture (770 mg) of 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid methyl ester and diacyl body was obtained. This mixture was dissolved in methanol (30 ml), concentrated hydrochloric acid (1 ml) was added and it was refluxed for three hours. The solvent was eliminated by distillation, and methylene chloride and 1 N aqueous sodium bicarbonate were added to the residue. The organic layer was washed with water, dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography, and 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid methyl ester was obtained.

(0032)

6-(3,5-di-tert-butylphenyl carboxamide) methylnicotinate (93 mg) was dissolved by heating to methanol (10 ml). 2 N NaOH (2 ml) was added, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was acidified by adding 2 N HCl and thereafter solvent was eliminated by distillation. To the residue were added ethyl acetate and water, the organic layer was separated and was washed with saturated aqueous sodium chloride solution, dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was recrystallised from methanol / ethyl acetate, and 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid was obtained.

Colourless prism crystals, mp >300 degrees.

1H NMR (400 MHz, DMSO-d6, 30 degrees) delta: 11.27 (s, 1H), 8.89 (d, 1H, J = 2.2 Hz), 8.34 (d, 1H, J = 8.4 Hz), 8.31 (dd, 1H, J = 2 Hz, 8.5 Hz), 7.87 (d, 1H, J = 1.5 Hz), 7.63 (brt, 1H), 1.34 (s, 18H)

Elemental analysis (C21H26N2O3): theoretical value C 71.16; H 7.39; N 7.90, experimental value C 71.19; H 7.66; N 7.88.

(0033)

Example 4: 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid.

5-methoxycarbonyl pyridine-2-carboxylic acid (14 g) was dissolved in benzene (120 ml) and thionyl chloride (85 ml) was added, and it was refluxed for four hours. The solvent was eliminated by distillation, anhydrous benzene was added to the residue, thionyl chloride was eliminated by distillation and acid chloride was obtained. Benzene solution of aforesaid acid chloride (170 ml) was dropwise-added at 20 degrees to pyridine (62 ml) - benzene (100 ml) solution of 3,5-di-tert-butyl aniline (14.9 g) and it was reacted for three hours. The reaction liquor was discharged into iced water (120 ml), 1 N HCl (57 ml) was added and it was extracted twice with ethyl acetate (60 ml). The organic layer was washed successively with 0.5 N HCl (150 ml) and saturated aqueous sodium chloride solution (150 ml x twice), and it was dewatered with anhydrous magnesium sulphate. It was treated with activated charcoal (850 mg), and the solvent was eliminated by distillation, and 26.8 g residue was obtained. It was recrystallised from mixed solvent of n-hexane and ethyl acetate, and ester of 22.5 g was obtained.

(0034)

Aforesaid ester was suspended in methanol (280 ml), and 2 N NaOH (125 ml) was added at 20 degrees or less and it was reacted at room temperature for six hours. 1.5 N HCl (150 ml) was added at 20 degrees or less and precipitated crystals were extracted with ethyl acetate 1.5 l. After washing, ethyl acetate was eliminated by distillation and residue was recrystallised from ethyl acetate - ethanol, and 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid 14.7 g was obtained. mp. 288-289.5 degrees.

(0035)

(2) Production Example of topical agent.

Example 1: Toner.

6-(3,4-diethylphenyl carbamoyl) nicotinic acid	0.05
2-hydroxy -4-methoxybenzo phenone-5-sodium sulphonate	0.1
Acetic acid tocophenol	0.01
Glycerine	4.0
1, 3-butylene glycol	4.0
Ethanol	8.0
Polyoxyethylene (60) hardened castor oil	0.5
Methyl para pen	0.2
Citric acid	0.05
Citric acid soda	0.1

Flavour	0.05
Purified water	balance

(0036)

2-hydroxy-4-methoxybenzo phenone-5-sodium sulphonate, citric acid, citric acid soda, glycerine and 1,3-butylene glycol were dissolved in purified water. Separately, polyoxyethylene (60) hardened castor oil, acetic acid tocophenol, flavour and methyl paraben were dissolved to 6-(3,4-diethylphenyl carbamoyl) nicotinic acid and ethanol, and this solution was added to aforesaid solution and a toner was obtained by filtration.

(0037)

Example 2: cream.

Cetostearyl alcohol	3.5
Squalane	40.0
Beeswax	3.0
Reduction lanolin	5.0
Ethylparaben	0.3
Polyoxyethylene (20) sorbitan mono palmitate	2.0
Stearic acid monoglyceride	2.0
N-stearoyl sodium glutamate	0.5
2-hydroxy -4-methoxybenzo phenone	0.5
Methoxy cinnamic acid octyl	1.0
Retinol acetate	2.0
Evening primrose oil	0.05
Flavour	0.03
6-(3,4-diethylphenyl carboxamide) nicotinic acid	0.1
1,3-butylene glycol	5.0
Polyethyleneglycol 1500	5.0
Purified water	balance

(0038)

Cetostearyl alcohol, squalane, beeswax, reduction lanolin, ethylparaben, polyoxyethylene (20) sorbitan mono palmitate, stearic acid monoglyceride, N-stearoyl sodium glutamate, 2-hydroxy-4-methoxybenzo phenone, methoxycinnamic acid octyl, retinol acetate, evening primrose oil and 6-(3,4-diethylphenyl carboxamide) nicotinic acid were dissolved by heating, and this was added while stirring to purified water together with 1,3-butylene glycol and polyethyleneglycol 1500 which were separately warmed to 75 degrees. It was processed with a homo mixer, the emulsified particles were made fine, thereafter it was rapidly cooled while stirring, and cream was obtained.

(0039)

Example 3: Milky lotion

6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid	0.2
Para dimethylaminobenzoic acid -2-ethylhexyl	0.1
Dipara methoxy cinnamic acid mono -2-ethylhexyl	0.2
Stearic acid	1.5
Cetyl alcohol	0.5
Beeswax	2.0
Polyoxyethylene (10) monoolein acid ester	2.0
L-arginine	0.3
L-glutamate Na	0.02
PCA-Na	0.05
Hyaluronate Na	0.01
Propylene glycol	5.0
Glycerine	3.0
Ethanol	3.0
Ethylparaben	0.3
Flavour	0.03
Carboxy vinyl polymer	0.12
Purified water	balance.

(0040)

Flavour was added to ethanol and was dissolved (alcohol phase). On the other hand, L-arginine, L-glutamate Na, PCA-Na, hyaluronate Na, propylene glycol, glycerol, carboxy vinyl polymer were added to purified water and were dissolved by heating, and it was held at 70 degrees (aqueous phase). Furthermore, other components were mixed and dissolved by heating, and it was kept at 70 degrees (oil phase). The oil phase was added to the aqueous phase, preliminary emulsification was carried out, and it was uniformly emulsified with a homo mixer. While stirring this mixture, alcohol phase was added, thereafter it was cooled to 30 degrees while stirring, and amilky lotion was obtained.

(0041)

Example 4: foam mask.

6-(3,5-di-tert-butylphenyl carboxamide)-nicotinic acid	0.02
4-tert butyl-4'-methoxy-dibenzoyl-methane	0.5
Stearic acid	1.0
Behenic acid	1.0
Self emulsification type monostearic acid glycerol	1.5
Monostearic acid polyoxyethylene (5) glycerol	2.5
Batyl alcohol	1.5
Flavour	0.05
Glycerine	5.0
1,3-butylene glycol	5.0
Polyethyleneglycol 1500	3.0
Methylparaben	0.1
Potassium hydroxide	0.15
Purified water	balance
Liquefied petroleum gas	6.0
Dimethylether	2.0.

(0042)

Glycerol, 1,3-butylene glycol, polyethyleneglycol 1500, methylparaben, potassium hydroxide were added to purified water and dissolved by heating at 70 degrees. Other components except for liquefied petroleum gas and dimethylether were dissolved by heating and added to this solution, it was uniformly mixed, and packed into a container. Finally liquefied petroleum gas and dimethylether were added as propellant, and foam mask was obtained.

(0043)

Example 5: ointment.

6-(3,4-diethylphenyl carbamoyl) nicotinic acid	0.1
Para dimethylaminobenzoic acid octyl	4.0
Butyl methoxybenzoyl methane	4.0
Tocopheryl acetate	0.5
Palmitic acid retinol	1.0
Stearyl alcohol	18.0
Japan wax	20.0
Polyoxyethylene (10) monoolein acid ester	0.25
Glycerol monostearic acid ester	0.3
Vaseline	32.0
Purified water	balance.

(0044)

Purified water was kept at 70 degrees (aqueous phase), on the other hand, other components were mixed and dissolved at 70 degrees (oil phase). The oil phase was added to aqueous phase, it was uniformly emulsified with a homo mixer, thereafter it was cooled, and ointment was obtained.

(0045)

(3) Test examples.

Example 1: Action on EGF dependent proliferation of fibroblast.

Proliferation of fibroblast whose proliferation is arrested under low serum condition, is dependent on the growth factor, and the proliferation is promoted with addition of EGF, and when retinoic acid is caused to be co-present further proliferation promotion is performed. Therefore the action on EGF dependent proliferation of fibroblast was examined with respect to the component of topical agent of this invention. PDL12 cells obtained by subculturing human skin fibroblast (HF52) was suspended in 5% FBS-DMEM, inoculated to dish of a diameter of 3.5 cm (47,200 /dish), and cultured at 37 degrees for seven hours, and thereafter the medium was replaced with a culture medium in which DMSO or test compound of prescribed concentration was added to 0.25% FBS-DMEM containing 4 nM EGF, and it was cultured for seven days. The DNA quantity of cells was determined by fluorescence method, and proliferation acceleration ratio was determined.

(0046)

The results are shown in Figure 1. The EGF dependent proliferation was promoted by 40-50 % by the co-presence retinoic acid of 10 [power -6] M concentration. Using the EGF dependent proliferation by this retinoic acid as index, retinoid action of aforesaid compound was examined. As

a result, 6-(3,4-diethylphenyl carbamoyl) nicotinic acid showed proliferation promotion action by 30 % at 10 [power -5] M and by 20 % at 10 [power -6] M, and 6-(3,4-diethylphenyl carboxamide) nicotinic acid showed proliferation promotion action of 20 % at 10 [power -6] M.

(0047)

Example 2:. Flattening action of hairless mouse skin surface configuration (hide furrow) by topical application.

By topical application or internal administration of retinoic acid, skin assumes a reddish tinge and is changed to a glossy and transparent state. Utilising that similar phenomenon can be reproduced with hairless mouse, the action of topical agent of this invention was compared with retinoic acid using a quantitative index corresponding to the change thereof. Retinoic acid acetone solution of 0.05 %, 0.025 % and 0.01 %, and each 1 % acetone solutions of 6-(3,4-diethylphenyl carbamoyl) nicotinic acid, 6-(3,4-diethylphenyl carboxamide) nicotinic acid, 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid and 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid shown in Production Examples, and acetone were respectively applied onto hairless mouse for 30 days (5 times / weeks), and replica of skin surface was cast using silicon series resin on the following day of the final application day, and the various kinds of parameters showing the characteristics of skin surface configuration were determined using image analysis apparatus.

(0048)

By repeated application of retinoic acid, the skin changed concentration dependently to a skin with a reddish tinge and gloss, and retinoid skin-like change observed in human, was produced. Hide crest disappeared on replica with respect to this change, and it was regarded as the change that surface became flattened. It is known that the image analysis parameter KSD (dispersion of luminance distribution in KSD = 3.9 mm x 3.9 mm) is correlated to hide furrow depth (contemporary dermatology system • yearly edition 90B), and this value corresponded well with the action of retinoic acid (Table 1). In each case, the compounds obtained with Production Examples produced retinoic acid-like changes, and although weaker than retinoic acid, KSD change was observed. In histological examination, the inflammatory changes (cell infiltration within dermis and epidermis, intercellular • intracellular edema, vasodilation and the like) found in retinoic acid were not observed in any of the test compounds. The clearest change was acanthosis (Table 2)

(0049)

(Table 1)

KSD change (%)

Acetone	89.7%
0.01 % retinoic acid	79.2 %
0.025 % retinoic acid	73.4 %
0.05 % retinoic acid	33.6 %
1 % 6-(3,4-diethylphenyl carbamoyl) nicotinic acid	84.5 %
1 % 6-(3,4-diethylphenyl carboxamide) nicotinic acid	83.7 %
1 % 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid	78.3 %
1 % 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid	76.9 %

(0050)

(Table 2)

	Acanthosis (μm)
Acetone	18 μm
0.01 % retinoic acid	48 μm
1 % 6-(3,4-diethylphenyl carbamoyl) nicotinic acid	22μm
1 % 6-(3,4-diethylphenyl carboxamide) nicotinic acid	21 μm
1 % 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid	32 μm
1 % 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid	35 μm

(0051)

Example 3: Action with respect to rhinomouse skin.

On the epidermis of the rhinomouse, egg shaped cysts (utricle) that contain keratin derived from trichocyst are present. This egg shaped cyst is known to shrink due to retinoic acid administration (doe example, Ashton, R. E. et al, J. Invest. Dermatol., 82, pp. 632-635, 1984 and the like). The aforesaid action was examined with respect to the compounds shown in Production Examples. Test compound solution of prescribed concentration and carrier 0.1 ml were applied onto dorsal skin of 8 week old female rhinomouse in a frequency of once or twice per day, 5 days per week over two week period. For the purpose of histological evaluation, the dorsal skin was excised, the epidermis was separated from the dermis using 0.5 % acetic acid, and epidermis sheet for light microscopy observation was produced. The image data obtained via CCD camera was analysed, and the area of egg shaped cysts was determined. The results are shown in Table 3. The retinoic acid showed strong skin flare, but skin flare was not observed at all with the compounds shown in Production Examples.

(0052)

(Table 3)

	Decrease of egg shaped cysts area (vs carrier, %)					
	0.00001 %	0.0001 %	0.001%	0.01 %	0.1 %	1 %
Retinoic acid	77	59	15			

1% 6-(3,4-diethylphenyl carbamoyl) nicotinic acid	90	87	60
1% 6-(3,4-diethylphenyl carboxamide) nicotinic acid	95	89	50
1% 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid	80	62	40
1% 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid	81	58	30

(0053)

Example 4: Metabolic Test.

One of the reason why the retinoic acid shows toxicity in human, is that the retinoic acid is hard to be metabolised. Therefore, the metabolism of two types of the compounds shown in Production Examples was evaluated by the following method. The test substance which was dissolved in ethanol was added to a buffer containing a specified quantity of rat liver homogenate (25 % homogenate in which rat liver 25 g from which blood was eliminated by irrigation with 0.15 M KCl solution was homogenised with 75 ml phosphate-buffered liquid of pH 7) (final concentration 10 [power -4] M), and the residual quantity of test substance was determined with time by HPLC. The results are shown in Table 4. From the obtained results, it was indicated that the compounds of this invention were readily metabolised in vivo.

(0054)

(Table 4)

Metabolism in rate liver homogenate

Compound	Residual quantity after 10 min. (%)	Residual quantity after 60 min. (%)
6-(3,4-diethylphenyl carbamoyl) nicotinic acid	65	5.0
6-(3,4-diethylphenyl carboxamide) nicotinic acid	55	3.0

*t = 0 as 100 %

(0055)

Example 5: stability test

Ethanol solution of each compound 300 ppm obtained in Production Examples was irradiated with xenon light for 30 hours, or was stored at 50 degrees two months, thereafter the residual quantity was determined by HPLC. As a result, all the compound was confirmed to be remaining by 95 % or more. On the other hand, retinoic acid was rapidly decomposed under the same conditions.

(0056)

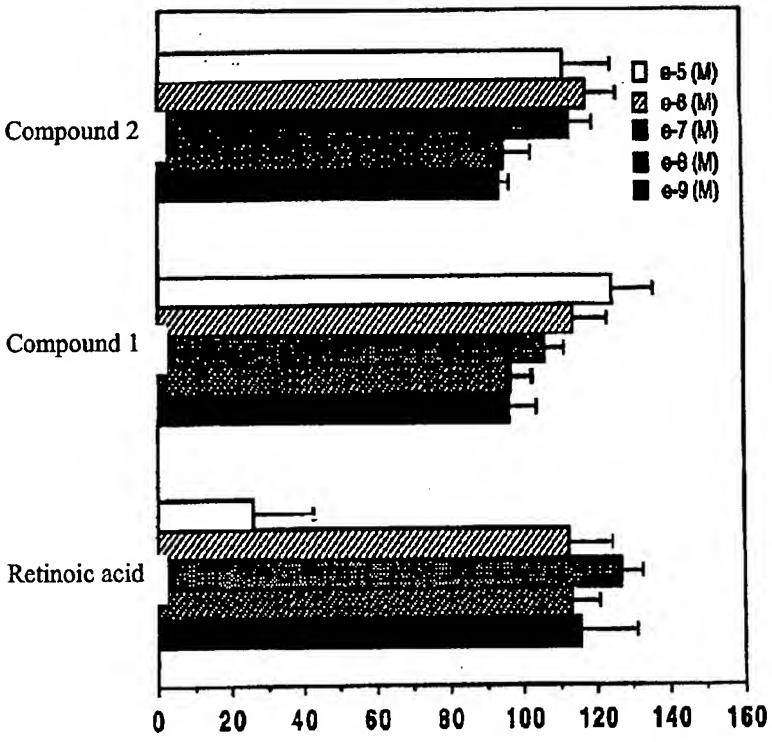
(Advantages Afforded by this Invention)

The compound of aforesaid formula which is a component of topical agent of this invention has excellent skin deterioration prevention action, and, in addition, it is stable, percutaneous absorption is small, and safety is high. Moreover, even when absorbed in body, it is readily metabolised, therefore, there is a characteristic that side effect due to retinoid action is not caused.

(Brief Description of the Figures)

(Figure 1) It is a figure showing the action of representative compounds contained in topical agent of this invention on the EGF dependent proliferation of fibroblast. Compound 1 in figure shows 6-(3,4-diethylphenyl carbamoyl) nicotinic acid, and compound 2 shows 6-(3,4-diethylphenyl carboxamide) nicotinic acid.

(Figure 1)



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